Remarks

Claims 26, 29-30, 42-44, 46, and 48 have been amended for technical clarity and commercial purposes. Claims 47 and 49 have been cancelled. Claims 50-53 have been added. Claims 23-26, 29-31, 42-44, 46, 48, and 50-53 are currently pending in the instant application.

Support for claim 50 is found in the present application on pages 27-30, 40-41, and 44-45. Support for claim 51 is found in claim 42 and cancelled claim 49. Support for claim 52 is found in claim 43. Support for claim 53 is found in claim 46.

Claim 47 has been cancelled without prejudice or disclaimer and with reservation of the right to pursue the subject matter of this claim in later cases. The cancellation of claim 47 was not prompted by any rejection in the Office Action.

Claim 49 has been cancelled without prejudice or disclaimer and the subject matter of cancelled claim 49 has been included in claim 51.

I. § 112 Rejection

Claim 47 was rejected under 35 U.S.C. § 112, second paragraph, as being indefinite on the basis that it is unclear how a protein hybridizes to a sequence of the ligation product as required in claim 42. In the interest of furthering prosecution, claim 47 has been cancelled without prejudice or disclaimer and with reservation of the right to pursue the subject matter of this claim in later cases.

II. § 103 Rejections

Independent claim 42 was rejected as being unpatentable over Nikiforov et al. (U.S. Patent 5,952,174) ("Nikiforov") in view of Weisburg et al. (U.S. Patent 6,110,678) ("Weisburg").

Claim 42 is directed to a method of determining the identification of a nucleotide at a detection position in a target sequence. The method includes providing a hybridization complex including a target sequence and two primers. The method further includes providing an extension reaction and a ligation reaction to form a ligation product. The method further includes detecting the ligation product by providing microspheres comprising a capture probe that hybridizes to a sequence contained within the ligation product.

In contrast, Nikiforov discloses a ligase/polymerase mediated method of detecting a nucleotide at a preselected site of a target sequence. The method includes immobilizing a first

ligation probe to a solid support that will hybridize to a region of a target sequence, then adding a second ligation probe that will hybridize to a second region of the target. The first and second probes are separated by a single nucleotide. Following hybridization there are two reactions: one of extension of one of the ligation probes and then ligation of both probes. The ligation product is immobilized and detected. Nikiforov requires stable hybridization between the first and second probes and the target sequence, meaning hybridization that has a T_m greater than the temperature under which the interrogation assay is to be run. See Nikiforov, col. 12, ll. 4-9. Nikiforov does not teach the use of microspheres on the surface of a substrate. Further, Nikiforov fails to teach first and second capture probes that hybridize to first and second sequences contained within the first and second ligation products, respectively.

Weisburg discloses a method of capturing a target polynucleotide in a sample onto a solid support with an attached immobilized probe by using a capture probe. That is, Weisberg teaches the use of two different sequences for attachment of the target, thus resulting in a complex of three oligomers. Weisberg further requires two different hybridization conditions. See Weisburg, col. 2, ll. 8-22. The two hybridization conditions control the order of hybridization, where the first hybridization conditions allow hybridization of the capture probe to the target polynucleotide, and the second hybridization conditions allow hybridization of the capture probe to the immobilized probe. Weisburg does not teach first and second capture probes that hybridize to first and second sequences contained within the first and second ligation products, respectively.

The Examiner states that it would have been obvious to one of ordinary skill in the art to modify the capture of Nikiforov by providing microspheres having capture probes which hybridize to the extension product as taught by Weisburg to thereby optimize environmental conditions for each method step as suggested by Weisburg for the obvious benefits of maximizing experimental results. Applicant respectfully traverses.

A. Independent Claim 42 Is Not Made Obvious by Nikiforov in View of Weisburg Because There Is No Motivation to Combine the References

1. There Is No Motivation to Combine the Cited References Because the Cited Motivation Is Legally Incorrect

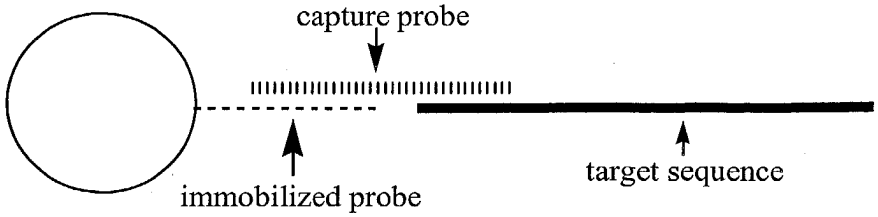
As the Examiner undoubtedly knows, "[i]n determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference

teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination, or other modification." In re Linter, 458 F.2d 1013, 1016 (CCPA 1972). Further, there must be a finding "as to the *specific understanding or principle* within the knowledge of the skilled artisan" that provides the motivation to combine the two references. In re Kotzab, 217 F.3d 1365, 1371 (Fed. Cir. 2000).

There is no *specific understanding or principle* set forth in the Office Action providing motivation to combine Nikiforov and Weisburg. Instead, it is stated in the Office Action that it would have been obvious for one of ordinary skill in the art to combine the references to optimize environmental conditions for each method step as suggested by Weisburg "for the obvious benefits of maximizing experimental results." Applicant is puzzled about the meaning of "maximizing experimental results." Instead of a specific understanding or principle, there is essentially an alleged motivation to combine Nikiforov and Weisburg based on some generic reasoning involving some mysterious maximization of experimental results. This reasoning is legally incorrect. Thus, there is no motivation for one having ordinary skill in the art to combine Nikiforov and Weisburg. Accordingly, claim 42 stands in condition for allowance.

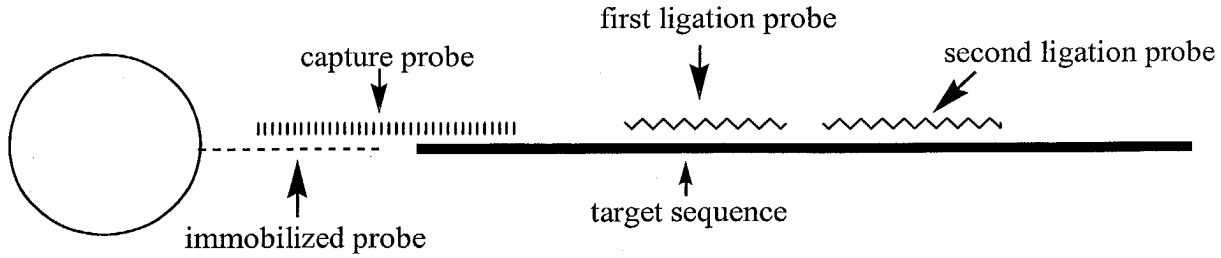
2. There Is No Motivation to Combine the Cited References Because the Combination Does Not Maximize Experimental Results

Even assuming, arguendo, that maximization of experimental results *were* a proper motivation for combining the references, such a combination would be undesirable because the additional oligonucleotides required in the combination are detrimental to the maximization of experimental results. As discussed above, Weisburg teaches the use of two probes (the "immobilized" and "capture" probes) to capture a target sequence. The resulting composition is depicted as follows:



Weisburg alone, therefore, requires only three oligonucleotides.

The combination of Weisburg with Nikiforov, however, would require a minimum of five oligonucleotides. That is, the combination would include the target sequence, the "immobilized" and "capture" probes of Weisburg, and the first and second ligation probes of Nikiforov, which is depicted as follows:



The combination would require adding two additional oligonucleotides to perform the reaction successfully. One of ordinary skill in the art would recognize that the requirement for additional oligonucleotides means additional steps and time to add the additional oligos and perform the reaction, thus potentially resulting in a *minimizing* of experimental results. Thus, one of ordinary skill would find no motivation to or expectation of success in combining Weisburg and Nikiforov. Claim 42, therefore, is in condition for allowance.

B. Independent Claim 42 Is Not Made Obvious by Nikiforov in View of Weisburg Because Nikiforov Teaches Away from the Combination

As discussed above, Nikiforov requires hybridization that has a T_m greater than the temperature under which the interrogation assay is to be run. That is, Nikiforov teaches that the reaction temperature be at a level which allows for hybridization. Thus, Nikiforov requires that the temperature be maintained at a level at which hybridization of the oligonucleotides in the reaction freely occurs. See Nikiforov, col. 12, ll. 4-9. Weisburg, however, requires the alteration of the reaction conditions such that hybridization is selectively inhibited in order to perform both steps of its reaction. See Weisburg, col. 6, ll. 32-63. Thus, the temperature requirements of Nikiforov teach away from combination with Weisburg. Further, the combination of the two references could be rendered inoperable by the differing temperature requirements. Thus, Nikiforov teaches away from the combination with Weisburg. Claim 42, therefore, stands in condition for allowance. Reconsideration and withdrawal of the rejections is respectfully requested.

D. Claims Depending From Claim 42 Are Patentable

Because claims 23-26, 29-31, 43-44, 46, and 48 depend directly or indirectly from claim 42 and incorporate all the limitations of claim 42, the above arguments obviate the basis for this ground of rejection. Thus, claims 23-26, 29-31, 43-44, 46, and 48 are not made obvious by Nikiforov in view of Weisburg. Reconsideration and withdrawal of the rejection is respectfully requested.

E. Dependent Claim 29 Is Not Made Obvious by Nikiforov in View of Weisburg and Further in View of Walt

Dependent claim 29 was rejected as being unpatentable over Nikiforov in view of Weisburg and further in view of Walt et al. (U.S. Patent 6,327,410) ("Walt").

It is alleged in the Office Action that Walt is directed to a method of target detection comprising "providing a substrate with a surface comprising discrete sites, further comprising a population of microspheres comprising at least a first and second subpopulation wherein each subpopulation comprises a capture probe and wherein the substrate is a fiber optic bundle wherein the fiber optic bundle substrate provides 'extremely high density' substrate for detection of an extremely high number of targets." Office Action, p. 9, ll. 6-12. It is respectfully submitted that claim 29 is not made obvious by Nikiforov in view of Weisburg and further in view of Walt.

1. There Is No Motivation to Combine the Cited References Because the Combination Does Not Maximize Experimental Results

There is no motivation to combine Walt with Nikiforov and Weisburg because Walt fails to overcome the problems of combining Nikiforov and Weisburg. As explained above, there is no motivation to combine Nikiforov and Weisburg because the additional oligonucleotides required in the combination are detrimental to any maximization of experimental results. Walt fails to address this problem, because the combination of the three references would still require a minimum of five oligonucleotides, while Weisburg alone requires only three. One of ordinary skill in the art would recognize that the requirement for additional oligonucleotides means additional steps and time to add the additional oligos and perform the reaction, thus potentially resulting in a *minimizing* of experimental results. Thus, one of ordinary skill would find no motivation to or expectation of success in combining Walt with Nikiforov and Weisburg. Claim 29, therefore, is in condition for allowance.

2. Claim 29 Is Not Made Obvious Because Nikiforov Teaches Away from the Combination

As discussed above, Nikiforov teaches away from the combination with Weisburg. That is, Nikiforov requires that the temperature of the reaction be maintained at a level at which hybridization of the oligonucleotides in the reaction freely occurs. In contrast, Weisburg teaches the alteration of the reaction temperature such that hybridization is selectively inhibited in order to perform both steps of its reaction. Thus, the temperature requirements of Nikiforov teach away from combination with Weisburg.

Walt fails to overcome the deficiencies of Nikiforov and Weisburg because Walt, like Nikiforov, teaches that the temperature be maintained at a level at which hybridization of the oligonucleotides can occur. See Walt, col. 11, ll. 2-5. Walt, therefore, has temperature requirements that teach away from the combination with Weisburg.

Thus, the temperature requirements of Nikiforov and Walt teach away from combination with Weisburg. Further, the combination of the three references would be rendered inoperable by the differing temperature requirements. Claim 29, therefore, stands in condition for allowance. Reconsideration and withdrawal of the rejections is respectfully requested.

F. Rejection of Dependent Claim 49 As Being Made Obvious by Nikiforov in View of Weisburg and Further in View of Walt

Because dependent claim 49 was cancelled for reasons unrelated to the present rejection, this rejection no longer applies.

G. Secondary Considerations of Commercial Success

It is stated in the Office Action that Applicant has not shown a nexus between Illumina's commercial success and the presently claimed invention. Applicant respectfully traverses.

1. Illumina's Use of Claimed Invention in HapMap Project

There is a clear nexus between the claimed invention and the commercial success of Illumina's platform. In addition to the evidence previously provided, the commercial success of Illumina's platform is evidenced by Illumina's participation in the International HapMap Project ("HapMap"). As explained in the June issue of the *MIT Technology Review* (enclosed herein as Exhibit A), HapMap is a project organized by the world's top genetic researchers, including the National Institutes of Health ("NIH") and Johns Hopkins University, to chart a map of "common haplotype patterns among a number of the world's population groups." *MIT Technology Review*,

Vol. 6, No. 5, June, 2003, p. 42 (Exhibit A). Further explanation of the project is provided on the NIH's National Human Genome Research Institute website at http://www.genome.gov/10005336, enclosed herein as Exhibit B. Please note that the NIH states in its explanation that the project requires the use of "robust technologies" that "must be capable of high throughput, high quality and low cost." As further shown on the NIH website at http://www.genome.gov/10005338 (enclosed herein as Exhibit C), Illumina is one of only *five* institutions in the United States participating in the project.

The nexus between the commercial success reflected by Illumina's participation in HapMap and the presently claimed invention is set forth in *Technology Review*. The publication explains that Illumina's platform as used in HapMap comprises the use of an optical fiber array in which each fiber is capped with a silica bead coated with DNA probes, wherein different DNA sequences in the test samples bind to the probes on each particular bead. *See MIT Technology Review*, p. 44 (inset).

As can be seen, the above evidence involves *no advertising*. On the contrary, this evidence is comprised of information provided in an article in a highly respected publication for cutting-edge technology and from the NIH website. As the Examiner will appreciate, the NIH is a highly respected institution not swayed by "mere advertising". There is, therefore, a clear nexus between the claimed invention and the commercial success of Illumina's platform.

The evidence above is further bolstered by the fact that other of the select institutions involved in the HapMap project have purchased Illumina's platform for use in charting the map. As a result, *more than fifty percent* of the map in this worldwide project is being charted with Illumina's platform. See Illumina Press Releases of April 23, 2003, http://www.shareholder.com/illumina/news/20030423-107323.cfm?ReleaseType=Earnings (enclosed herein as Exhibit D) and June 30, 2003 http://www.shareholder.com/illumina/news/20030630-112514.cfm?ReleaseType=General (enclosed herein as Exhibit E). This remarkable statistic is not based on promotion or advertising. Regardless of whether the statistic is provided in a press release or an article, it is evidence of the *fact* that over fifty percent of the sequence mapping in a project organized by the world's top genetic researchers is being performed using Illumina's platform. These highly-educated, top scientists require a robust, high-throughput technology for this elite project and

thus could never be swayed by mere promotional elements in identifying Illumina's platform as meeting their stringent requirements. Further, the present technology is "not the kind of merchandise that can be sold by advertising hyperbole." Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1383-84 (Fed. Cir. 1986). Thus, it is respectfully submitted that the commercial success of Illumina's platform is related solely to the presently claimed invention. The present rejection, therefore, is improper.

If the Examiner is still not satisfied that the above new information provides sufficient evidence of a nexus between the commercial success of Illumina's platform and the presently claimed invention, Applicant is willing to provide an additional declaration setting forth in detail the use of the claimed invention in HapMap. The Examiner is invited to contact the undersigned Attorney at 415-781-1989 to request such a declaration or any additional information regarding Illumina's use of its presently claimed invention in HapMap.

2. Illumina's Prior Evidence Is Sufficient to Establish Commercial Success

Applicant respectfully submits that the previously submitted evidence of commercial success *does* present sufficient evidence for a finding of commercial success.

Though it is stated in the Office Action that the required nexus between the commercial success of Illumina's platform and the presently claimed invention has not been established, the previously submitted evidence establishes such a nexus. The Examiner is referred to the Declaration of John Stuelpnagel, which states that the claimed method is the method used to do genotyping at Illumina.

The portion of the Stuelpnagel Declaration that seems to be the focus of the Office Action is the statement that Illumina "utilizes the methods outlined in the claims." This language is rejected in the Office Action because language attributing commercial success to a process "constructed according to the disclosure and claims" does not establish a nexus. However, Applicant invites the Examiner to examine the statements set forth by Stuelpnagel above the offending language. In those statements, Stuelpnagel refers *specifically* to the claimed invention, stating that the present system "utilizes labeled probes that are part of a hybridization complex with a capture probe on a surface" and further states that "ligation and extension assays are currently run." This is not generic language attributing success to a process constructed

"according to the application." Rather, these specific statements detail the elements of the platform and how they relate to the claimed invention. The required nexus, therefore, has been established and the burden is now on the challenger to adduce evidence to show that the commercial success is due to extraneous factors other than the patented invention. See Demaco Corp. v. F. Von Langsdorff Licensing Ltd., 851 F.2d 1387, 1393.

The commercial success of Illumina's platform is clearly not the result of advertising and promotion. In fact, Applicant is somewhat bewildered by the repeated references to advertising in the Office Actions. As discussed above, it is well-established and has been noted by Applicant in prior responses that the present technology is "not the kind of merchandise that can be sold by advertising hyperbole." Hybritech, 802 F.2d at 1383-84. As such, it is respectfully submitted that any promotional element of the previously submitted evidence has no bearing on the commercial success of Illumina's platform, and hence that the present rejection is improper.

In conclusion, it is respectfully submitted that claims 23-26, 29-31, 42-44, 46, and 48 -49 are not obvious. Reconsideration and withdrawal of the rejections is respectfully requested.

II. Double Patenting Rejection

Claims 29-31, 42-43, and 46-48 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 and 27-30 of U.S. Patent 6,355,431. It is respectfully requested that this rejection be held in abeyance until otherwise allowable subject matter is found.

Conclusion

Applicant respectfully submits that claims 23-26, 29-31, 42-44, 46, and 48 are in condition for allowance. Reconsideration and a Notice of Allowance for all pending claims is respectfully requested. Please direct any calls in connection with this application to the undersigned attorney at 415-781-1989.

Respectfully submitted,

DORSEY & WHITNEY LLP

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